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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/579,290 | 05/15/2006 | Heinz Vollmers | 043043-0359295 | 7070 |

27500 7590 09/19/2008

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| EXAMINER | |
|---|---|
| BRISTOL, LYNN ANNE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1643 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 09/19/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/579,290 | VOLLMERS ET AL. | |
| | Examiner | Art Unit | |
| | LYNN BRISTOL | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *72-91 and 95-116* is/are pending in the application.

4a) Of the above claim(s) *89-91 and 95-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-79, 82-88 and 98-116* is/are rejected.

7)☒ Claim(s) *80 and 81* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/15/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 72-91 and 95-116 are all the pending claims for this application.

2. Claims 92-94 were cancelled and new Claims 98-116 were added in the Reply of 6/2/08.

3. The copy of the English language priority document, EP 03026161.4, provided with the filing of 6/2/08 is acknowledged.

4. The preliminary amendment to the specification filed on 4/21/08 to insert the deposit information for the SAM-6- producing hybridoma has been considered and entered.

### *Election/Restrictions*

5. Applicant's election with traverse of Group I (Claims 72-88) as to Claims 95-97 (Group IV) in the reply filed on 6/2/08 is acknowledged. The traversal is on the ground(s) that Claims 95-97 (original Group IV) have been amended to depend from Claim 72; the nucleic acid would encode a heavy or light chain variable region sequence of the antibody of Claim 72; and searching Group I will necessarily overlap with a search of Claims 95-97 without undue burden.

This is not found persuasive because Claim 72 (antibody) now links the inventions for a nucleic acid (Claim 95), a vector (Claim 96) and a cell comprising the vector (Claim 97). Upon the allowance of the linking claim, the restriction requirement as to the linked invention(s) shall be withdrawn and any claims depending from or otherwise including all the limitations of the allowable linking claims will be entitled to

examination in the instant application. Applicants are advised that if any such claims depending from or including all the limitations of the allowable linking claims is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or non-statutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-132 (CCPA 1971). See also MPEP § 804.01..

The requirement is still deemed proper and is therefore made FINAL.

6. Claims 89-90 and 95-97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on 6/2/08.

7. Claims 72-88 and 98-116 are all the pending claims under examination.

***Information Disclosure Statement***

8. The U.S., international and foreign patent references and the non-patent literature references cited in the IDS of 3/15/07 have been considered and entered with the exception of the following reference #'s: LR-PR and RR because the references are in German language and a translation of the abstract and/or relevant portions has not been provided; UR and KKR because a copy of the reference was not provided with the IDS filing; and GGGGR because only a foreign language copy was filed. Reference

XXXR is not a non-patent literature reference and has been stricken from the section of the 1449 form indicating such and inserted under the foreign patent documents section as reference UUR. The initialed 1449 is attached hereto.

***Specification***

9. The disclosure is objected to because of the following informalities:

a) The specification does not cross-reference the related priority applications. Please note that the priority applications cannot be incorporated by reference after the original filing of the instant application. For additional information on claiming benefit to an earlier filed application see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application".

b) The use of trademarks, e.g., Cytoxan®, has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

c) The figure legend to Figures 10A and 10B is objected to for failing to describe the x- and y-axis labels for each of the panels. Alternatively, Applicants can amend Figure 10 to label the axes.

Appropriate correction is required.

### *Claim Objections*

10. Claims 72 and 75 are objected to for the following informalities:

a) The phrase “an adenocarcinoma of the esophagus” is recited in duplicate for both Claims 72 and 75;

b) The phrase "a diffuso-type gastric carcinoma" appears to be a typographical error in Claim 75.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

### *Enablement*

11. Claims 72-79, 82-88 and 98-116 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the full SAM-6 antibody comprising SEQ ID NO:1 (VL) and SEQ ID NO:3 (VH) and/or binding fragments comprising the VL/VH and which bind the O-linked carbohydrate moiety on a post-transcriptionally modified isoform of the 78-kDa GRP, designated $GRP78^{SAM-6}$, does not reasonably provide enablement for any antibody with binding specificity for the antigen and having: at least 75%, 80%, 85%, 90% or 95% identity to either the VL of SEQ ID NO:1 and/or the VH of SEQ ID NO:3, or a single VL domain (SEQ ID NO:1) or a single VH domain (SEQ ID NO:3), or a single CDR domain or less than the full complement of VL CDR1-3 and VH CDR1-3. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention/ Skill in the Art

The claims are interpreted as broadly encompassing of an antibody or antigen binding fragment thereof with binding specificity for the antigen expressed on an adenocarcinoma of the lung, squamous cell lung carcinoma, intestinal type gastric carcinoma, diffuse type gastric carcinoma, adenocarcinoma of the colon, adenocarcinoma of the prostate, squamous cell carcinoma of the esophagus, adenocar cinoma of the esophagus, lobular carcinoma of the breast, ductal carcinoma of the breast, adenocarcinoma of the pancreas, adenocarcinoma of the ovary, and adenocarcinoma of the uterus, or that it binds to the following cell lines: BXPC-3, 23132/87, COLO-206F, COL0-699 or LOU-NH91, and where the antibody has: at least 75%, 80%, 85%, 90% or 95% identity to either the VL of SEQ ID NO:1 and/or the VH of SEQ ID NO:3, or a single VL domain (SEQ ID NO:1) or a single VH domain (SEQ ID

NO:3), or a single CDR domain or less than the full complement of VL CDR1-3 and VH CDR1-3 from SEQ ID NO:1 and/or SEQ ID NO:3.

The relative skill in the art required to practice the invention is a molecular immunologist.

Disclosure in the Specification

The specification generally contemplates making antibodies on p. 29, line 16 to p. 34, line 21; generating antibody variants by DNA modifications on p. 34, line 23 to p. 36, line 26. The specification provides definitions for functional antibody fragments (p. 14, lines 14-25).

The specification discloses a single isolated antibody, SAM-6, selected from a library of antibodies generated by fusing lymphocytes from a human stomach adenocarcinoma patient (Table 1) with the heteromyeloma cell line HAB-1 to produce a trioma. At the time of filing, Applicants specification did not reveal the identity of the antigen but generally characterized the antigen immunohistochemical screening of SAM-6 against normal tissues and autologous tumor where the antigen was defined by the cancer cell-binding properties for the antibody (Example 2). SAM-6 showed no reactivity with normal tissues but different tumor tissues (Tables 3 and 4). Partial characterization of the antigen in Example 3 showed by Western blot analysis the antibody recognized proteins of 140 kDa (Figure 3A). Rauschert et al (Lab. Invest. 88:375-386 (2008)) later described the antigen as GRP78 and the epitope is an O-linked carbohydrate moiety. The sequence for SAM-6 was determined for VL and VH (Example 2). Sam-6 antibody was shown to induce apoptosis in the cell lines BXPC-3

and 23132/87 (Example 4); and inhibit proliferation of the cell line 23132/87 (Example 5).

The specification contemplates but does not specifically disclose working embodiments for just any of the antibody structures encompassed by the claims much less that any modified antibody would have the required properties of recognizing an adenocarcinoma of the lung, squamous cell lung carcinoma, intestinal type gastric carcinoma, diffuse type gastric carcinoma, adenocarcinoma of the colon, adenocarcinoma of the prostate, squamous cell carcinoma of the esophagus, adenocar cinoma of the esophagus, lobular carcinoma of the breast, ductal carcinoma of the breast, adenocarcinoma of the pancreas, adenocarcinoma of the ovary, and adenocarcinoma of the uterus, or that it binds to the following deposited cell lines: BXPC-3, 23132/87, COLO-206F, COL0-699 or LOU-NH91.

Without sufficient guidance in the written description alone, the ordinary artisan could not practice making and using the myriad antibody embodiments encompassed by the claims because the specification and claims do not define which regions and domains are subject to variation, which regions or domains could tolerate the introduction of the variation, or the nature and extent of the variation. For example, the claims are not limited to whether the extent of variation comprises amino acid substitutions, insertions, deletions and combinations thereof so that the ordinary artisan could predict which variation would not compromise antigen binding specificity. The claims are not limited as to whether the variation occurs in the antigen binding domains or Fc regions, or the CDRs and/or framework domains. Thus it is not readily apparent

from the specification or the original claims as filed, how the ordinary artisan could practice the invention without incurring undue experimentation in order to identify a reasonable number of working embodiments based on the extent of antibody variation encompassed by the claims. Further, the claims encompass antibody embodiments having structures that are generally viewed in the field of art as being non-operative or at least unpredictable as to their antigen affininty, namely, antibodies having single variable domains or those having fewer than the full complement of both VL and VH CDRs. Thus the ordinary artisan could not reduce to practice the myriad embodiments and expect to obtain a reasonable number of working embodiments absent undue experimentation at the levels of gene manipulation, antibody screening and bioassay performance.

Prior Art Status: Single CDR-domain Antibodies

The claims encompass isolated antibodies comprising a single CDR domain (and less than the full complement of VH/VL CDRs) from SAM-6 antibody. Applicants have not shown that any isolated any antibody comprising less than a full complement of VH/VL CDRs from a parent SAM-6 antibody would retain the antigen binding to any on the cell lines test in the assays. In fact there are numerous publications acknowledging that the conformation of CDRs as well as framework residues influence binding.

MacCallum *et al.* (J. Mol. Biol. 262:732-745 (1996)) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs

coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

de Pascalis *et al.* (Journal of Immunology 169, 3076-3084 (2002)) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset *et al.* (BBRC 307, 198-205, (2003)) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* (J. Mol. Biol. 320, 415-428 (2002)) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Holm *et al* (Mol. Immunol. 44: 1075-1084 (2007)) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Chen *et al.* (J. Mol. Bio. 293, 865-881 (1999)) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Wu *et al.* (J. Mol. Biol. 294, 151-162 (1999)) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Thus, while one can make the statement that a single CDR makes a significant contribution in the antigen binding, the residues in these CDRs are not the only residues that influence binding and in fact the prior art as well as applicants own disclosure do not support that it was clearly established, that the a single CDR domain alone is sufficient to define the binding specificity of an antibody, and that multiple antibodies can predictably be generated having the same binding specificity based on a single CDR (or less than full complement of VH CDRs and VL CDRs).

Analyzing applicants own disclosure, which while it does contemplates divergent CDR residues, the only working example is the SAM-6 antibody having heavy chain

CDRs paired with complementary light chain CDRs. Additionally, the data indicate that it is the frameworks and CDRs that contribute to antigen binding. Further, there are no examples of mixing or matching of the light chain CDRs or heavy chain CDRs and most importantly there is no working example of placing a single CDR domain of a heavy chain and/or a light chain in just any framework and producing an antibody that binds antigen as broadly claimed or suggested.

Prior Art Status: Conservative Amino Acid Substitutions within CDR/FR Residues

The claims encompass antibodies comprising VH domains, VL domains and CRDs which vary in the extent to which they resemble the corresponding domain in the parent SAM-6 antibody. This variation can comprise any number and kind of amino acid substitutions. It is not well established in the art that all variable domains are amenable to modifications much less that that substitutions are for conservative amino acids. Numerous publications acknowledge that conservative substitutions would in fact change the binding ability of antibodies if not substantially reduce the affinity.

Brummell *et al*. (Biochemistry 32:1180-1187 (1993)) found that mutagenesis of the four HCDR3 contact residues for the carbohydrate antibody (Salmomella B O-polysaccharide) in no instance improved affinity but 60% of the mutants resulted in a 10-fold drop in binding constant (affinity electrophoresis value of 0.85), while still other mutants were lower (Table 1 and p. 1183, Col. 2, ¶2 to p. 1184, Col. 1, ¶1). Brummell demonstrates that no substitution retained antigen binding affinity similar to the wild type antibody despite targeted, conservative substitutions in known contact sites.

Kobayashi *et al.* (Protein Engineering 12:879-844 (1999)) discloses that a scFv for binding a DNA oligomer containing a (6-4) photoproduct with Phe or Tyr substitutions at Trp 33 retained "a large fraction of the wild-type binding affinity, while the Ala substitution diminished antigen binding" (Table 1). However, Kobayashi notes "replacing Trp 33 with Phe or Ala alters the local environment of the (6-4) photodimer since binding is accompanied by large fluorescence increases that are not seen with the wild-type scFv" (p. 883, Col. 2, ¶3).

Burks *et al.* (PNAS 94:412-417 (1997)) discloses scanning saturation mutagenesis of the anti-digoxin scFv (26-10) which also binds digitoxin and digoxigenin with high affinity and with 42-fold lower affinity to ouabain. 114 mutant scFvs were characterized for their affinities for digoxin, digitonin, digoxignenin and oubain. Histogram analysis of the mutants (Figure 2) reveals that "not all residues are optimized in even high affinity antibodies such as 26-10, and that the absence of close contact with the hapten confers higher plasticity, i.e., the ability to tolerate a wider range of substitutions without compromising binding (p. 415, Col. 2, ¶4- p. 416, ¶1).

Brummell *et al*., Kobayashi *et al.* and Burks *et al.* introduced conservative amino acid substitutions into CDRs to examine binding effects and demonstrate that any conservative substitution within any CDR cannot be made without affecting binding.

Jang *et al.* (Molec. Immunol. 35:1207-1217 (1998)) teach that single amino acid mutations to the CDRH3 of a scFV derived from 2C10, an anti-dsDNA autoantibody, reduced the binding activity about 20-50% compared to the unmutated scFv (Table 4).

Brorson *et al.* (J. Immunol. 163:6694-6701 (1999)) teach that single amino acid substitutions to the CDRs of IgM Abs for the bacterial protein, levan, are ablated.

Coleman (Research in Immunol. 145:33-36 (1994)) teaches that single amino acid changes within the interface of an antibody-antigen complex are important and that inasmuch as the interaction can tolerate amino acid sequence substitutions, "a very conservative substitution may abolish binding" while "in another, a non-conservative substitution may have very little effect on the binding" (p. 35, Col. 1, ¶1).

Prior Art Status for Single Variable Domain Antibodies

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding.

Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which

maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Unpredictability/Undue Experimentation

The specification provides no direction or guidance regarding how to produce the genus of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Furthermore, while the level of skill required to generate the antibodies is that of a molecular immunologist, the ordinary artisan would have been required to identify candidate amino acid residues for substitution in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant ($K_D$), dissociation and association rates ($K_{off}$ and $K_{on}$ respectively), and binding affinity and/or avidity compared with the parent antibody) in a BIAcore assay, and then finally perform bioassays to identify any one or more of the characteristics of the antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR amino acid substitutions encompassed by the claims would result in *just any* substituted antibody clone having retained the antigen binding activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is

merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

***Conclusion***

12. No claims are allowed.

13. The VL (SEQ ID NO:1) and VH (SEQ ID NO:3) domains of the SAM-6 antibody are free from prior art.

14. Claims 80 and 81 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Examiner, Art Unit 1643
Temporary Partial Signatory Authority